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09/338,855	06/23/99	SORGE J	04435/79243

EXAMINER	
CHAKRABARTI,A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/338,855	Sorge
Examiner	**Art Unit**
Arun Chakrabarti	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Aug 28, 2001 .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-3, 57-74, and 145-156 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-3, 57-74, and 145-156 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Specification

1. Claims 1, 57 and 69 have been amended.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claims 1-3 and 150-153 are rejected under 35 U.S.C. 102 (a) as being anticipated by Oefner et al. (U.S. Patent 5,795,976) (August 18, 1998).

Oefner et al. teach a method of enriching for and identifying a nucleic acid sequence difference with respect to a reference sequence and a method for accessing a sub-portion of a nucleic acid population (Abstract), comprising:

a) hybridizing a nucleic acid sample with a nucleic acid molecule comprising a sequence-specific binding activity under conditions which permit specific binding, wherein the sample comprises a subset of nucleic acid molecules having a sequence that binds to the sequence-specific binding activity, and wherein a bound subset of nucleic acid molecules is retained by the sequence-specific binding activity, such that the subset of bound nucleic acid molecules is enriched for molecules comprising the sequence recognized by the sequence specific binding activity (Column 9, lines 39-43, Example 2 and Column 13, line 21 to column 17, line 12); and

b) detecting a sequence difference with respect to a reference sequence in the subset of nucleic acid molecules (Column 18, lines 1-30 and Example 7, column 34, lines 7-13, Example 8, column 34, line 53 to column 36, line 27 and Figures 11A and 11B).

Oefner et al. teach a method wherein the molecule comprising sequence-specific binding activity is selected from nucleic acid molecules (Abstract, Column 22, line 59 to Column 24, line 58).

Oefner et al. teach a method wherein the sequence-specific binding activity is bound to a solid support (Examples 2, 3, 4, 5, 6 and 8 and Figures 1-4 and 6-13).

Oefner et al. teach a method of enriching for and identifying a nucleic acid sequence difference with respect to a reference sequence (Abstract), comprising:

a) fragmenting a nucleic acid sample from one or more individuals (Column 9, lines 39-43);

b) physically separating a subset of the nucleic acid fragments based on the size of the fragments (Example 2 and Column 13, line 21 to column 17, line 12);

c) operatively linking the subset of step (b) with molecules capable of being replicated (Column 13, line 21 to column 17, line 12);

d) introducing the linked subset of molecules of step c) into a system capable of replicating the linked subset of molecules, and replicating the subset of linked molecules to form an enriched collection of replicated molecules (Column 17, lines 14-67).

e) detecting one or more nucleotide sequence differences in the members of the collection of step (d) with a method capable of detecting one or more nucleotide differences with respect to a reference sequence (Column 18, lines 1-30 and Example 7, column 34, lines 7-13, Example 8, column 34, line 53 to column 36, line 27 and Figures 11A and 11B).

Oefner et al. teach a method wherein the system capable of replicating the linked molecules comprises host cells and the collection of replicated molecules comprises a library (Column 22, line 59 to Column 24, line 58).

Oefner et al. teach a method wherein the system capable of detecting one or more nucleotide conformational differences comprises DNA sequencing by electrophoresis (Column 35, lines 3-27).

Oefner et al. teach a method wherein the method capable of detecting one or more nucleotide difference comprises denaturing HPLC (Examples 2, 3, 4, 5, 6 and 8 and Figures 1-4 and 6-13).

Oefner et al. teach a method wherein the method capable of detecting one or more nucleotide difference comprises a protein capable of detecting mismatches between duplexed strands of nucleic acid (Column 23, lines 45-56).

Oefner et al. teach a method wherein the steps (a)- (b) are repeated one or more times to increase the enrichment of the enriched collection of repeated molecules (Example 7).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-3, 57-74, and 145-155 are rejected under 35 U.S.C. 103 (a) over Oefner et al. (U.S. Patent 5,795,976) (August 18, 1998) in view of Bloch et al (U.S. Patent 5,866,429) (February 2, 1999) .

Oefner et al teach the method of claims 1-3 and 150-153 as described above.

Oefner et al do not teach the fragmenting a nucleic acid sample by endonuclease digestion.

Bloch et al teach the fragmenting a nucleic acid sample by restriction endonuclease digestion (Example 1, column 19, lines 58-64).

Bloch et al teach the fragmenting a nucleic acid sample with one or more sequence - specific cleavage agents restriction endonuclease to produce nucleic acid fragments (Example 1, column 19, lines 58-64). Bloch et al teach the method wherein at least one restriction endonuclease cleaves DNA infrequently (Example 4, column 24, lines 5-8).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine within the method of comparative hybridization and sequencing of Oefner et al., the method of restriction endonuclease digestion

of Bloch et al. since Bloch et al state, "Another preferred method, used alone or together with PCR, for providing nucleic acid suitable for HPLC analysis is digestion with a restriction endonuclease , a procedure which, for relatively homogeneous DNA, generates a finite and often low number of well defined fragments (Column 13, lines 20-24)". An ordinary artisan would have been motivated by the express statement of Bloch et al to substitute and combine the model of restriction endonuclease digestion of Bloch et al with the methods of comparative hybridization and sequencing of Oefner et al. in order to achieve the express advantages, as noted by Bloch et al. , of a method which for relatively homogeneous DNA, generates a finite and often low number of well defined fragments.

6. Claims 1-3, 57-74, and 145-156 are rejected under 35 U.S.C. 103 (a) over Oefner et al. (U.S. Patent 5,795,976) (August 18, 1998) in view of Bloch et al (U.S. Patent 5,866,429) (February 2, 1999) further in view of Fox et al. (U.S. Patent 6,140,086) (October 31, 2000).

Oefner et al. in view of Bloch et al teach the method of claims 1-3, 57-74, and 145-155 as described above.

Oefner et al. in view of Bloch et al do not teach the method wherein the infrequently cleaving restriction endonuclease is selected from NotI.

Fox et al teach the method wherein the infrequently cleaving restriction endonuclease is selected from NotI (Column 17, lines 46-67).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine within the method of comparative

hybridization and sequencing of Oefner et al in view of Bloch et al., the method of NotI restriction endonuclease digestion of Fox et al. since Fox et al state, "Restriction endonucleases that may be advantageously used in the methods of the invention include, but are not limited to AluI, Eco47 III, -- , NotI, PstI, PuvI, SacI/SstI, SalI, XbaI, XhoI and I-CeuI. Such restriction endonucleases are available commercially (Column 17, lines 57-64)". An ordinary artisan would have been motivated by the express statement of Fox et al to substitute and combine the method of NotI restriction endonuclease digestion of Fox et al. with the method of comparative hybridization and sequencing of Oefner et al in view of Bloch et al., in order to achieve the express advantages, as noted by Fox et al. , of a restriction endonuclease which may be advantageously used in the methods of cloning nucleic acid molecules and which are available commercially.

Response to Amendment

7. In response to amendment, all 112 (second paragraph) rejections are withdrawn. However, all 102 and 103 rejections are hereby being maintained.

Response to Arguments

8. In response to applicant's argument that the Oefner and Bloch references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies

(i.e., A) subset of nucleic acid molecules are less than every molecule in the population, B) fragmenting of nucleic acid molecules cannot be generated by synthesis or amplification, C) infrequent cutting of the nucleic acids to generate an average fragment size of 10,000 bp or greater or that it cleaves a given mammalian genome 300,000 times or fewer) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant also argues that order of performing the steps of claim 57 in Oefner reference are not same as the invention of claim 57. This argument is not persuasive. However, MPEP 2144.04 further states, " *In re Gibson,* 39 F.2d 975, 5 USPQ 230 (CCPA 1930) Selection of any order of mixing ingredients is *prima facie* obvious". Therefore, 102 (a) rejection with regard to claim 57 has been withdrawn and is now rejected as obvious over Oefner et al. in view of Bloch et al.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant also argues that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Bloch et al. since Bloch et al state, "Another preferred method, used alone or together with PCR, for providing nucleic acid suitable for HPLC analysis

is digestion with a restriction endonuclease , a procedure which, for relatively homogeneous DNA, generates a finite and often low number of well defined fragments (Column 13, lines 20-24)".

Therefor, in view of the response to argument, 102 (a) and 103(a) rejections are hereby properly maintained.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti , Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0195.

Arun Chakrabarti,

Patent Examiner,

September 5, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

9/5/01